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Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis

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Summary

Background: Statins are the most widely prescribed drug available. Due to this reason, it is important to understand the risks involved with the drug class and individual statins.

Aim: We conducted a meta-analysis and employed indirect comparisons to identify differing risk effects across statins.

Design: We included any randomized clinical trial (RCT) of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin used for cardiovascular disease event prevention. The main outcome was adverse events [all-cause mortality, cancers, rhabdomylosis, diabetes, aspartate and alanine aminotransferase (AST/ALT), and creatinine kinase (CK) increases beyond the upper limit of normal]. In order to evaluate the relative effects of each drug on adverse events, we calculated adjusted indirect comparisons of the adverse-event outcomes.

Results: Seventy-two trials involving 159 458 patients met our inclusion criteria. Overall, statin treatments significantly increased the rate of diabetes when compared to controls (OR: 1.09; 95% CI: 1.02–1.16) and elevated AST (OR: 1.31; 95% CI: 1.04–1.66) and ALT (OR: 1.28; 95% CI: 1.11–1.48) levels when compared to controls. Using indirect comparisons, we also found that atorvastatin significantly elevated AST levels compared to pravastatin (OR: 2.21; 95% CI: 1.13–4.29) and simvastatin significantly increased CK levels when compared to rosuvastatin (OR: 4.39; 95% CI: 1.01–19.07). Higher dose studies had increased risk of AST elevations.

Discussion: Although statins are generally well tolerated, there are risks associated with almost all drugs. With few exceptions, statins appear to exert a similar risk across individual drugs.

Introduction

HMG-CoA reductase inhibitors (statins) first appeared commercially in the late 1970s to treat high blood cholesterol levels and have gained widespread acceptance since they have demonstrated important reductions in cardiovascular morbidity and overall mortality.[1] Since then, statins have been extensively studied in a large variety of patient populations, including both primary and secondary prevention of cardiovascular disease (CVD).[2,3] Due to their effectiveness, there is a widespread interest in the use of statins for broad populations and two of them (simvastatin and pravastatin) are available in generic form. Statins may one day be widely

available over the counter (OTC).[4] Already, a 10 mg tablet of simvastatin is on sale OTC in the UK. Statins are also a component of the poly-pill, a combination strategy to reduce cardiovascular morbidity using cholesterol lowering, blood pressure lowering and blood thinning drugs.[5]

Since statins are prevalent in use, it is imperative to understand the risks involved with taking these medications. Known adverse events with statin therapy range from raised liver enzymes in some patients to potentially fatal rhabdomyolysis in rare occurrences, as occurred with cerivastatin before it was taken off the market in 2001.[6] Although these events are well documented, recent evidence suggests that statins can slightly increase the risk of developing diabetes mellitus.[7] Large, up-to-date systematic reviews with meta-analyses are essential to provide clinicians, health economists and policy makers with the most reliable, critically appraised and precise estimates of treatment effects and to monitor for rare adverse events. Therefore, we updated previous meta-analyses of statin trials[3,8–15] in an effort to assemble the totality of published randomized control trial (RCT) evidence to date, in order to assess adverse events associated with the use of individual statin treatments.

Methods

Eligibility criteria

We included any RCT of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin for CVD event prevention. Cerivastatin was not included, as it has been withdrawn from the market due to serious adverse events.[6] Studies had to compare a statin to placebo, standard therapy or no-treatment and report on any of the following clinically important cardiovascular outcomes: all-cause mortality; CVD mortality; fatal myocardial infarction (MI); non-fatal MI and major CV events (stroke, revascularization). We excluded studies only reporting on surrogate outcomes (e.g. LDL and HDL levels) and follow-up studies where randomization had been subverted. We additionally excluded head-to-head statin evaluations as we have reported these elsewhere.[16]

Search strategy

In consultation with a medical librarian, we established a search strategy (available from authors upon request). We searched independently, in duplicate, the following 12 databases (from inception to December 2010: MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science, databases that included the full text of journals, ScienceDirect and Ingenta, including articles in full text from ~1700 journals since 1993). In addition, we searched the bibliographies of published systematic reviews[3,8–15] and health technology assessments.[17–19] Finally, we searched our own comprehensive rolling database of statin trials, updated annually. We also contacted the authors of all trials for study clarifications, where required, and the authors of the only individual patient data meta-analysis of statins that included 14 trials.[14,15] Searches were not limited by language, sex or age.

Study selection

Two investigators (E.M., P.W.) working independently, in duplicate, scanned all abstracts and obtained the full-text reports of records that indicated or suggested that the study was a RCT evaluating statin therapy on the outcomes of interest. After obtaining full reports of the candidate trials (either in full peer-reviewed publication or press article), the same reviewers independently assessed eligibility from full-text papers.

Data collection

The same two reviewers conducted data extraction independently using a standardized pre-piloted form. The reviewers collected information about the statin and type of interventions tested, the population studied (age, sex and underlying conditions), the treatment effect on specified outcomes and the length of follow-up. Study evaluation included general methodological quality features, including sequence generation, blinding, use of intent-to-treat analysis, percentage of follow-up and allocation concealment.[20] We extracted data on the incidence of the following clinically relevant adverse-event outcomes: all-cause mortality, cancers, rhabdomyolosis, diabetes, aspartate aminotransferase (AST), aspartate aminotransferase (ALT) and creatinine kinase (CK). We determined when an individual study reported *a priori* the adverse events they would collect and thresholds to define them. We entered the data into an electronic database such that duplicate entries existed for each study; when the two entries did not match, we resolved differences through discussion and consensus.

Data analysis

In order to assess inter-rater reliability on inclusion of articles, we calculated the phi (ϕ) statistic that provides a measure of inter-observer agreement

independent of chance.[21] For mortality outcomes, we calculated the relative risk (RR) and appropriate 95% confidence intervals (95% CIs) of outcomes according to the number of events reported in the original studies or substudies intent-to-treat analyses. Where studies did not report intent to treat, we analyzed outcomes as all-patients randomized.[22] In the case of an individual patient data meta-analysis of 14 trials, we included outcomes as reported by the meta-analysis, in correspondence with the study's authors. In the event of zero-outcome events in one arm of a trial, we applied the Haldane method and added 0.5 to each arm.[23] We pooled studies as an analysis of all-statins combined using the DerSimonian–Laird random effects method,[24] which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability.[25] For non-mortality adverse events, we calculated event rates using Peto's odds ratio.[26] Peto's odds ratios appears to provide the least biased estimates and CI coverage with rare events.[27] Forest plots are displayed for each analysis, showing pooled estimates with 95% CIs, and the overall DerSimmonian–Laird pooled estimate. We tested for heterogeneity using the Cochran *Q*-test and calculated the I^2 statistic for each all-statin analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.[28] We conducted a multivariable meta-regression analysis to examine the impact of the following co-variates, all chosen *a priori*: absolute LDL change; proportion of individuals in trials that were men; had a history of CHD, had a diagnosis of diabetes or were hypertensive and current smokers at baseline.[29] We conducted a subgroup analysis examining high doses of statins on adverse events.

In order to evaluate the relative effects of each drug on adverse events, we calculated adjusted indirect comparisons of the adverse-event outcomes.[30] We previously evaluated the impact of adjusted indirect comparisons in reference to another strategy of evaluating indirect comparisons, the multiple treatment comparison meta-analysis and demonstrated that they yield similar estimates when dealing with star-shaped networks (where all drugs have a mutual control).[31] Analyses were conducted using StatsDirect (version 2.5.2, www.statsdirect.com) and the Canadian Agency for Drugs and Technology Indirect Comparison software (version 1).

Role of the funding source

No funding sources had a role in study design, data collection, data analysis, data interpretation or writing of the report. The writing group had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 72 RCTs met our inclusion criteria (Figure 1). Data were available on 159 458 participants. Appendix Table S1 displays the characteristics of included studies and Appendix Table S2 displays the criteria for defining adverse events and the studies that had *a priori* determined adverse events as reported in the methods section of individual RCTs. Women represented ~30% of trial participants. The mean age of included participants was 59.8 (SD 5.99) years, trial averages ranging from 39 to 75 years. Trials used placebo, usual care, no treatment or conventional therapy as inert controls. Trials followed patients for a mean of 2.7 years (SD 1.61), ranging from 0.5 to 6.1 years.

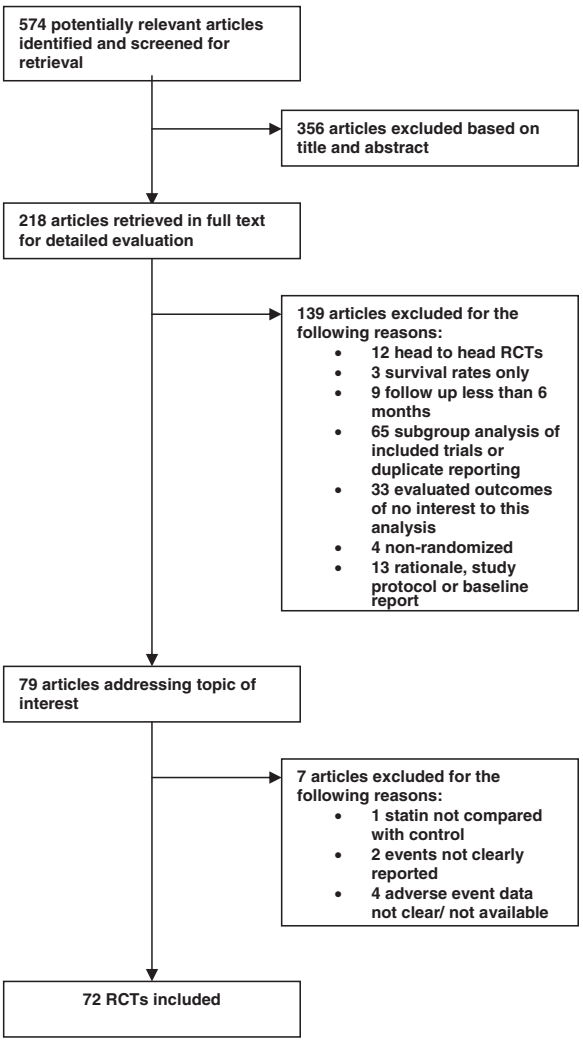

Figure 1. Study flow diagram.

The mean pre-treatment LDL cholesterol was 4.61 mmol/l (179.79 mg/dl) and ranged from 2.43 mmol/l (94.77 mg/dl) to 5 mmol/l (195 mg/dl).

Methodological quality of included studies

We found that the reporting quality of studies varied. Twenty-six studies reported how randomization sequence was generated in their primary publication. Nineteen studies reported on how allocation to groups was concealed. Sixty-four studies reported on loss to follow-up. Four studies reported that the primary results were based on a per-protocol analysis rather than intent to treat. Sixty-one studies reported on at least one specific group being blinded in the trial, typically patients and caregivers.

Deaths (all-cause)

There were a total of 13 577 deaths, including a total of 6898 from confirmed vascular causes. In all trials combined, there were a total of 6420 (7.4%) deaths among the 85 815 patients receiving a statin and 7157 (8.9%) deaths among 79 866 patients receiving a control intervention. In total, this represents an 11% reduction in all-cause mortality (RR: 0.89, 95% CI 0.86–0.93, $P \leqslant 0.0001$; $I^2 = 11\%$, $P = 0.21$).

Adverse events

Data on first incident cancers recorded after randomization were available from 33 RCTs.[1,32–63] The incidence of cancers was not different between statin groups and control groups [3706 (5.9%) vs. 3746 (6.0%); OR: 0.99, 95% CI 0.94–1.04, $P = 0.69$; $I^2 = 0\%$]. Rhabdomylosis information was available from 36 RCTs,[1,32–35,37–42,45–47,50–54,56,58,59,61,63–75] enrolling a total of 139 029 individuals. We did not find a significant difference between groups [179 (0.25%) statins vs. 170 (0.25%) controls; OR: 1.05, 95% CI 0.84–1.31, $P = 0.70$; $I^2 = 0\%$]. We evaluated incident diabetes available from 16 RCTs enrolling 118 240 individuals.[33,34,39–43,47,52,54–56,59,65,68,76] When we evaluated new incident diabetes, we found a significantly increased rate of diabetes [2246 (3.8%) statins vs. 2073 (3.5%) controls; OR: 1.09, 95% CI 1.02–1.16, $P = 0.015$; $I^2 = 11\%$]. We also examined the impact of statins on elevated AST from 22 RCTs[1,32–38,40,42,45,47,53,56,59,61,63,66,68,69,73,77] and found a significant association [OR: 1.31, 95% CI 1.04–1.66, $P = 0.022$; $I^2 = 42\%$]. The impact of statins on increased ALT levels from 20 RCTs[1,35,36,39,41–43,45–47,50–52,54,58,59,64,71,75,78] also showed a significant association [OR 1.28, 95% CI 1.11–1.48, $P \leqslant 0.001$; $I^2 = 0\%$]. The impact of statins on CK increases beyond normal from 26 RCTs[1,35–37,39–42,45–48,50,51,53,54,59,61,63,64,67–70,75,79] was not found to be significant [OR: 1.09, 95% CI 0.85–1.41, $P = 0.51$; $I^2 = 10\%$].

In a subgroup analysis examining exclusively high-dose statins, we found only an increased risk of adverse events on the end point of AST elevation. Cancer risk (two RCTs, OR 1.08, 95% CI 0.75–1.56, $P = -0.64$); rhabdomylosis (seven RCTs, OR 1.97, 95% CI 0.75–5.18, $P = 0.16$); diabetes (two RCTs, OR 1.22, 95% CI 1.05–1.43, $P = 0.01$); AST elevations (five RCTs, OR 3.53, 95% CI 2.02–6.16, $P \leqslant 0.0001$); ALT elevations (three RCTs, OR 1.43, 95% CI 0.65–3.14, $P = 0.36$) and CK elevations beyond normal (five RCTs, OR 0.91, 95% CI 0.12–7.01, $P = 0.93$). AST elevation was significantly different between lower and higher dose statins, diabetes incidence was not. Due to the small number of individual RCTs for each statin evaluating high doses, we did not find a significant effect for any individual statin.

Atorvastatin

The analysis of atorvastatin is shown in Table 1. Data on atorvastatin were available from 17 RCTs,[45,49,51,53,58,61,65,66,70,72–74,77,80–83] 6 of which had recorded the incidence of cancer after randomization in 11 763 patients. No significance was found for cancer incidence rates between treatment and control groups [185 (3.12%) statin vs. 205 (3.52%) controls; OR: 0.90, 95% CI 0.74–1.11, $P = 0.3214$; $I^2 = 0\%$]. Rhabdomyolysis information was available from 11 RCTs comprised of 26 067 patients. No significant difference was found between the treatment and control groups [13 (0.10%) statin vs. 9 (0.07%) controls; OR: 1.38, 95% CI 0.61–3.13, $P = 0.4436$; $I^2 = 0\%$]. No meta-analysis could be performed on the incidence of diabetes for atorvastatin as there was only one study that contained data on this. The effect of atorvastatin on elevated AST levels from six RCTs was found to be significant [83 (1.40%) statin vs. 32 (0.54%) controls; OR: 2.27, 95% CI 1.19–4.30, $P = 0.0123$; $I^2 = 41\%$], whereas the impact atorvastatin had on increased ALT levels [two RCTs; 22 (1.07%) statin vs. 15(0.73%) controls; OR: 1.74, 95% CI 0.50–6.07, $P = 0.3877$; $I^2 = \text{NA}$] and increased CK levels [five RCTs; 8 (0.18%) statin vs. 11 (0.24%) controls; OR: 1.21, 95% CI 0.19–7.92, $P = 0.84$; $I^2 = 56\%$] did not show any significant association.

Pravastatin

The analysis of pravastatin is shown in Table 2. Data on pravastatin were available from 25 RCTs

Table 1 Analysis of atorvastatin adverse events

Adverse effect	Random effects (DerSimonian–Laird)		I^2 (95% CI)
	Pooled odds ratio (95% CI)	*P*-value	
Cancer	0.902041 (0.735756–1.105906)	0.3214	0 (0–61)
Rhabdomyolysis	1.378303 (0.606514–3.132197)	0.4436	0 (0–61)
Diabetes mellitus	[a]	[a]	[a]
AST increase	2.266165 (1.194625–4.298842)	0.0123	40.5 (0–75.1)
ALT increase	1.735772 (0.496716–6.065652)	0.3877	NA
CK increase 10×	1.213217 (0.185757–7.923767)	0.84	55.90 (0–83.40)

[a]Denotes that not enough information was available to calculate an odds ratio.

Table 2 Analysis of pravastatin adverse events

Adverse effect	Random effects (DerSimonian–Laird)		I^2 (95% CI)
	Pooled ORs (95% CI)	*P*-value	
Cancer	1.030049 (0.954297–1.111813)	0.4475	0.0 (0.0–47.4)
Rhabdomyolysis	1.077021 (0.821407–1.412179)	0.5914	0.0 (0.0–56.3)
Diabetes mellitus	1.038997 (0.909307–1.187185)	0.5739	35.2 (0.0–69.0)
AST increase	1.026753 (0.85628–1.231165)	0.7756	0.0 (0.0–58.5)
ALT increase	1.087264 (0.849671–1.391295)	0.506	0.0 (0.0–67.9)
CK increase 10×	1.214801 (0.95896–1.5389)	0.1068	0.0 (0.0–61.0)

enrolling 55 470 patients.[33,34,40,43,44,46–48,55–57,59,60,63,68,71,84–92] For cancer, data were available from 14 RCTs and were made up of 50 770 patients [1436 (5.67%) statin vs. 1402 (5.52%) control; OR: 1.03, 95% CI 0.95–1.11, $P = 0.4475$; $I^2 = 0\%$]. For rhabdomyolysis, data were available from 10 RCTs made up of 40 394 individuals [120 (0.60%) statin vs. 114 (0.56%) controls; OR: 1.08, 95% CI 0.82–1.41, $P = 0.5914$; $I^2 = 0\%$]. For diabetes, data were available from nine RCTs made up of 46 190 patients [882 (3.83%) statin vs. 846 (3.66%) control; OR: 1.04, 95% CI 0.91–1.19, $P = 0.5739$; $I^2 = 35\%$]. For increased AST, data were available from seven RCTs made up of 35 350 patients [244 (1.38%) statin vs. 237 (1.34%) control; OR: 1.03, 95% CI 0.86–1.23, $P = 0.7756$; $I^2 = 0\%$]. For increased ALT, data were available from four RCTs made up of 15 200 patients [134 (1.77%) statin vs. 126 (1.65%) control; OR: 1.09, 95% CI 0.85–1.39, $P = 0.506$; $I^2 = 0\%$]. For a 10-fold increase in CK, data were available from seven RCTs made up of 26 407 patients [156 (1.19%) statin vs. 131 (0.99%) control; OR: 1.21, 95% CI 0.96–1.54, $P = 0.1068$; $I^2 = 0\%$]. No significant association between pravastatin and the listed adverse events was shown.

Fluvastatin

The analysis of fluvastatin is shown in Table 3. Data on fluvastatin were available from nine RCTs enrolling 7387 patients.[35–37,50,67,79,93–95] For cancer, data were available from four RCTs and were made up of 5042 patients [358 (14.24%) statin vs. 392 (15.53%) control; OR: 0.89, 95% CI 0.75–1.05, $P = 0.1696$; $I^2 = 0\%$]. For rhabdomyolysis, data were available from four RCTs made up of 5181 individuals [8 (0.31%) statin vs. 3 (0.12%) controls; OR: 2.68, 95% CI 0.68–10.55, $P = 0.1589$; $I^2 = $ N/A]. No meta-analysis could be performed on the incidence of diabetes for fluvastatin as there was no study that contained data on this. For increased AST, data were available from three RCTs made up of 2940 patients [15 (1.02%) statin vs. 6 (0.41%) control; OR: 2.46, 95% CI 0.93–6.52, $P = 0.071$; $I^2 = 0\%$]. For increased ALT, data were available from three RCTs made up of 3365 patients [20 (1.20%) statin vs. 15 (0.89%) control; OR: 1.38, 95% CI 0.62–3.07, $P = 0.4356$; $I^2 = 13.7\%$]. For a 10-fold increase

in CK, data were available from six RCTs made up of 5975 patients [4 (0.13%) statin vs. 8 (0.27%) control; OR: 0.60, 95% CI 0.18–2.03, $P = 0.4107$; $I^2 = 0\%$]. No significant association between fluvastatin and the listed adverse events was shown.

Lovastatin

The analysis of lovastatin is shown in Table 4. This meta-analysis included seven RCTs on Lovastatin that were made up of 16 753 individuals.[32,42,69,78,96–98] For the incidence of cancer after randomization, data were obtained from two RCTs, comprising 6875 people. No significant association was found between lovastatin and control groups [258 (7.53%) statin vs. 264 (7.71%) control; OR: 0.97, 95% CI 0.82–1.17, $P = 0.778$; $I^2 = $ N/A]. The impact of lovastatin on the incidence of rhabdomyolysis was presented in three RCTs made up of 15 120 patients. No significant association was found [7 (0.07%) statin vs. 2 (0.04%) control; OR: 1.33, 95% CI 0.27–6.58, $P = 0.7304$; $I^2 = 0\%$]. No meta-analysis could be performed on the incidence of diabetes for lovastatin as there was only one study that contained data on this. Three RCTs made up of 15 120 people provided data on the impact of lovastatin on increased AST levels, for which we found no statistically significant association [131 (1.31%) statin vs. 51 (1.00%) control; OR: 1.22, 95% CI 0.86–1.74, $P = 0.2714$; $I^2 = 0\%$]. Data on elevated ALT levels were available from two RCTs made up of 7524 people. The impact of lovastatin on raised ALT levels was found to be significant [116 (3.08%) statin vs. 76 (2.02%) control; OR: 1.54, 95% CI 1.15–2.07, $P = 0.0039$; $I^2 = $ N/A]. For a 10-fold increase in CK, data were available from two RCTs made up of 14 850 patients. There was no significant association found between lovastatin and a 10-fold increase in CK levels [38 (0.38%) statin vs. 28 (0.56%) control; OR: 0.85, 95% CI 0.52–1.40, $P = 0.5354$; $I^2 = $ N/A].

Rosuvastatin

The analysis of rosuvastatin is shown in Table 5. Data obtained for the analysis of rosuvastatin were made up of six RCTs, comprising 31 230 patients.[39,52,54,64,75,76] There were three RCTs made up of 25 586 individuals that recorded the incidence of cancer, for which we found no statistically significant association [561 (4.38%) statin vs. 576 (4.61%) control; OR: 0.97, 95% CI 0.86–1.09, $P = 0.6173$;

Table 3 Analysis of fluvastatin adverse events

Adverse effect	Random effects (DerSimonian–Laird)		I^2 (95% CI)
	Pooled ORs (95% CI)	*P*-value	
Cancer	0.890431 (0.754528–1.050813)	0.1696	0.0 (0.0–67.9)
Rhabdomyolysis	2.679039 (0.680016–10.554537)	0.1589	NA
Diabetes mellitus	[a]	[a]	[a]
AST increase	2.456471 (0.925877–6.517337)	0.071	0.0 (0.0–72.9)
ALT increase	1.375899 (0.616915–3.068653)	0.4356	13.7 (0.0–76.4)
CK increase 10×	0.600161 (0.177812–2.025697)	0.4107	0.0 (0.0–64.1)

[a]Denotes that not enough information was available to calculate an odds ratio.

Table 4 Analysis of lovastatin adverse events

Adverse effect	Random effects (DerSimonian–Laird)		I^2 (95% CI)
	Pooled ORs (95% CI)	*P*-value	
Cancer	0.974623 (0.815228–1.165183)	0.7779	NA
Rhabdomyolysis	1.32521 (0.26709–6.575247)	0.7304	0.0 (0.0–72.9)
Diabetes mellitus	[a]	[a]	[a]
AST increase	1.220048 (0.85596–1.739004)	0.2714	0.0 (0.0–72.9)
ALT increase	1.541269 (1.149376–2.066782)	0.0039	NA
CK increase 10×	0.853776 (0.517902–1.407474)	0.5354	NA

[a]Denotes that not enough information was available to calculate an odds ratio.

$I^2 = 0\%$]. Rhabdomyolysis information was available from five RCTs made up of 26 656 people and no significant association was found [7 (0.05%) statin vs. 13 (0.10%) control; OR: 0.73, 95% CI 0.17–3.09, $P = 0.6696$; $I^2 = 42\%$]. Data on the incidence of diabetes for rosuvastatin were available from four RCTs, comprising 30 160 people. There was a significant association between the use of rosuvastatin and incidence of diabetes [605 (4.01%) statin vs. 533 (3.54%) control; OR: 1.14, 95% CI 1.01–1.29, $P = 0.0318$; $I^2 = 1.5\%$]. No meta-analysis could be performed on elevated AST levels for rosuvastatin as there was no study that contained data on this. Information on elevated ALT levels was available from five RCTs made up of 26 656 people. The effect of rosuvastatin on ALT levels was not found to be significant [59 (0.44%) statin vs. 48 (0.37%) control; OR: 1.17, 95% CI 0.79–1.72, $P = 0.4345$; $I^2 = 0\%$]. Finally, there was no significant association found between rosuvastatin and a 10-fold increase in CK levels. Information was available from four RCTs, comprising 8854 individuals [5 (0.11%) statin vs. 8 (0.19%) control; OR: 0.52, 95% CI 0.16–1.64, $P = 0.2642$; $I^2 = 0\%$].

Simvastatin

The analysis of simvastatin is shown in Table 6. This meta-analysis included eight RCTs on simvastatin that were made up of 26 375 individuals.[1,38,41,62,99–102] Data on the incidence of cancer were available from four RCTs made up of 25 433 people. No significant association was found between simvastatin and the incidence of cancer [904 (7.11%) statin vs. 903 (7.10%) control; OR: 1.00, 95% CI 0.91–1.10, $P = 0.953$; $I^2 = 0\%$]. Rhabdomyolysis information was available from three RCTs made up of 25 361 patients and found no significant association [6 (0.05%) statin vs. 3 (0.02%) control; OR: 1.84, 95% CI 0.50–6.79, $P = 0.3611$; $I^2 = $ N/A]. For diabetes, data were available from two RCTs made up of 24 980 individuals. No significant association was found between simvastatin and the incidence of diabetes [533 (4.27%) statin vs. 486 (3.89%) control; OR: 1.10, 95% CI 0.97–1.25, $P = 0.1299$; $I^2 = $ N/A]. No meta-analysis could be performed on elevated AST levels for simvastatin as there was not enough information available. Data for elevated ALT levels were available from two RCTs, comprising 24 980 people. There

Table 5 Analysis of rosuvastatin adverse events

Adverse effect	Random effects (DerSimonian–Laird)		I^2 (95% CI)
	Pooled ORs (95% CI)	*P*-value	
Cancer	0.970027 (0.860884–1.093007)	0.6173	0.0 (0.0–72.9)
Rhabdomyolysis	0.730423 (0.172542–3.092107)	0.6696	42.3 (0.0–82.9)
Diabetes mellitus	1.142353 (1.011682–1.289902)	0.0318	1.5 (0.0–68.4)
AST increase	[a]	[a]	[a]
ALT increase	1.166338 (0.792951–1.715548)	0.4345	0.0 (0.0–64.1)
CK increase 10×	0.519735 (0.164764–1.639456)	0.2642	0.0 (0.0–72.90)

[a]Denotes that not enough information was available to calculate an odds ratio.

Table 6 Analysis of simvastatin adverse events

Adverse effect	Random effects (DerSimonian–Laird)		I^2 (95% CI)
	Pooled ORs (95% CI)	*P*-value	
Cancer	1.002891 (0.911183–1.103828)	0.953	0.0(0.0–67.9)
Rhabdomyolysis	1.838624 (0.497649–6.79302)	0.3611	NA
Diabetes mellitus	1.102552 (0.971698–1.251027)	0.1299	NA
AST increase	[a]	[a]	[a]
ALT increase	1.421204 (1.032603–1.956047)	0.031	NA
CK increase 10×	2.283946 (0.916175–5.69368)	0.0764	NA

[a]Denotes that not enough information was available to calculate an odds ratio.

was a significant association between simvastatin and increased ALT levels [92 (0.74%) statin vs. 65 (0.52%) control; OR: 1.42, 95% CI 1.03–1.96, $P = 0.031$; $I^2 = \text{N/A}$]. Finally, there was no significant link between the use of simvastatin and a 10-fold increase in CK levels. Data were available from two RCTs, comprising 24 980 patients [17 (0.14%) statin vs. 7 (0.06%) control; OR: 2.28; 95% CI 0.92–5.69, $P = 0.0764$; $I^2 = \text{N/A}$].

Indirect comparisons

After the analyses were performed on each of the different statins, they were compared to each other to determine if particular adverse events were significantly more likely to occur in one type of statin versus another type. It was found that atorvastatin is significantly more likely to lead to elevated AST levels versus pravastatin (OR: 2.21, 95% CI 1.13–4.29), and simvastatin is significantly more likely to cause a 10-fold increase in CK levels versus rosuvastatin (OR: 4.39, 95% CI 1.01–19.07) (Appendix Table S3). No other indirect comparisons were found to be associated with greater risk of developing adverse events.

Discussion

Overall, our meta-analysis showed that the use of statin therapy importantly decreased the risk of all-cause mortality. Statins were typically safe, although we did observe that the use of rosuvastatin was significantly associated with an increased rate of diabetes, the use of atorvastatin was significantly associated with elevated AST, and the use of lovastatin and simvastatin were significantly associated with elevated ALT. We also found possible differences between individual statins for the surrogate endpoints of AST and CK level changes.

The increased likelihood of developing diabetes with the use of statin therapy has recently received attention in the literature. Another meta-analysis conducted by Sattar *et al.* also found that statin treatments increase the risk of developing diabetes, although they concluded that the risk was low both in absolute terms and when compared with the reduction in coronary events.[103] Similar to our results, earlier meta-analyses have also shown significant increases in liver function tests with statins versus controls.[104,105] However, it is important to note that the recent results of a post hoc analysis of the GREACE study suggest that statins may exert beneficial effects also in patients with elevated transaminases.[106] Furthermore, our results indicated that simvastatin was only marginally significantly more likely to cause an increase in CK levels when compared to rosuvastatin. While others have failed to show significant CK elevations with statins,[104] a meta-analysis of head-to-head RCTs comparing high- and low-potency statins has shown a significant increase in CK with higher doses.[105]

There are several limitations to consider when interpreting the results of our analyses. Although there were large numbers of patients included in many of the source trials, power to differentiate across interventions may be considered a limitation. We were also limited by the quality of the source trial publications. Although we conducted a comprehensive search for trials to include in our meta-analysis, it is possible we may have missed relevant trials that are not published. In a similar way, trials may not report specific adverse events and so these outcomes cannot be evaluated in a meta-analysis. Additionally, it is possible that the data extracted from the included trials were originally reported incorrectly in the source publications. Furthermore, data were combined from multiple trials, each of which differed in patient populations and study design. However, this is a commonality in all meta-analyses, and we concluded that it was appropriate to pool these trials *a priori*.[107]

Our meta-analysis focused on specific adverse events overall as derived from the source trials. We cannot make any inferences on the impact of derivatives or other medications on statin metabolism and development of adverse events. In addition, our study does not make strong inferences on the dose effect of the individual statins on adverse events. In our study, AST and diabetes were significantly increased with higher doses, but only AST elevations remained significant compared with standard dosing. Adverse events associated with statin treatment may be more likely with higher doses of specific statins and with combination therapy.[16,105,108]

Adverse events less commonly reported in the source trial publications were not included in our meta-analysis. Our analysis focused only on mortality, cancers, rhabdomylosis, diabetes and abnormalities in AST, ALT and CK because these data were most consistently reported in the source trial publications. It is important to recognize that other, less-common adverse events may occur with the use of statin treatments. For example, transient proteinuria, glucose elevations, renal failure, sleep reductions and sexual dysfunction, among others, have also been reported as adverse events in RCTs evaluating the effect of statin treatments.[109]

In conclusion, since many government health departments have recently recommended that people

at intermediate risk of CVD begin taking statins, this could lead to further public health policy changes. Our study indicates that the use of statin therapy for CVD is associated with a relatively low risk of adverse events.

Supplementary Data

Supplementary Data are available at *QJMED* online.

Conflict of interest: None declared.

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